ORIGINAL ARTICLE

Screening for Addison's disease in patients with type 1 diabetes mellitus and recurrent hypoglycaemia

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Postgrad Med J 2007;**83**:420–421. doi: 10.1136/pgmj.2007.058321

Received 4 February 2007
Accepted 23 February 2007

Background: Addison's disease may present with recurrent hypoglycaemia in subjects with type 1 diabetes mellitus. There are no data, however, on the prevalence of Addison's disease presenting with recurrent hypoglycaemia in patients with diabetes mellitus.
Methods: Three year retrospective study of diabetic patients with ''unexplained'' recurrent hypoglycaemia investigated with a short Synacthen test to exclude adrenocortical insufficiency.
Results: 95 patients with type 1 diabetes mellitus were studied. Addison's disease was identified as the cause of recurrent hypoglycaemia in one patient with type 1 diabetes mellitus.
Conclusion: Addison's disease is a relatively rare but remedial cause of recurrent hypoglycaemia in patients with type 1 diabetes mellitus. A low threshold for investigating patients with type 1 diabetes mellitus and recurrent hypoglycaemia to detect Addison's disease is therefore suggested.

Addison's disease may present as recurrent hypoglycaemia in patients with type 1 diabetes mellitus[1–7] and it is recommended that diabetic patients with unexplained recurrent hypoglycaemia be screened for Addison's disease.[8] There are, however, no data on the prevalence of Addison's disease presenting with recurrent hypoglycaemia in patients with diabetes. We report on the prevalence of Addison's disease presenting with recurrent hypoglycaemia in patients with type 1 diabetes mellitus.

METHODS

In a 3 year retrospective study we studied the frequency of Addison's disease as a cause of recurrent hypoglycaemia in patients with types 1 diabetes mellitus. All patients had recurrent hypoglycaemic episodes which appeared unrelated to insulin treatment, meal plans, exercise patterns, alcohol consumption, co-morbidity and concurrent medication. Exclusion criteria included those receiving or who had recently received steroid treatment and those with known pituitary, liver, renal, asthma and malignant disease.

Short Synacthen tests, which can be carried out at any time of the day,[9] were performed in the afternoon. An intravenous cannula was inserted into an antecubital fossa vein and a baseline blood sample was collected between 14.00 and 14.30. A dose of 250 μg tetracosactide (Synacthen, Alliance Pharmaceuticals Ltd, Chippenham, UK) was then administered intravenously and further blood samples collected 30 and 60 min later. Blood was separated and serum cortisol measured by electrochemiluminescence immunoassay (Elecsys Cortisol, Roche Diagnostics GmbH, Mannheim, Germany) on the Roche Modular Analytics E170 immunoassay analyser. The assay has a detection limit of 2 nmol/l (Package insert, Elecsys Cortisol, Roche Diagnostics GmbH, Mannheim Germany). The inter-assay coefficient of variation for the cortisol assay is 1.7% at 410 nmol/l. Internal quality control and external quality assessment for cortisol were satisfactory throughout the study period. A normal cortisol response to Synacthen was defined as a post-stimulation peak cortisol value of ⩾500 nmol/l at either 30 or 60 min with an incremental cortisol response ⩾200 nmol/l.[9]

Since data had a normal distribution (Kolmogorov-Smirnov test), results are expressed as means with standard deviations (SD) in parentheses.

RESULTS

Synacthen tests were performed on 95 patients with type 1 diabetes mellitus and recurrent hypoglycaemia (table 1).

One subject, a 39-year-old man with type 1 diabetes mellitus, was diagnosed with autoimmune Addison's disease (peak cortisol 111 nmol/l; incremental cortisol 32 nmol/l; adrenocorticotropic hormone (ACTH) 449 ng/l; adrenal antibodies positive; normal thyroid function tests; negative thyroid microsomal antibodies). Hydrocortisone replacement therapy led to a resolution of hypoglycaemia, improved glycaemic control, re-instatement of his driving licence, and resumption of his job as a gas fitter.

DISCUSSION

Addison's disease occurs more frequently in patients with type 1 diabetes mellitus as part of the autoimmune polyendocrine syndromes.[10–14] The diagnosis of Addison's disease is, however, often delayed because the onset of diabetes mellitus usually precedes the diagnosis of Addison's disease.[10 14] Cortisol deficiency increases insulin sensitivity resulting in increased peripheral glucose utilisation, impaired gluconeogenesis and decreased hepatic glucose output.[15] Hypoglycaemia would, therefore, be expected to be a prominent and early feature of Addison's disease in diabetic patients on hypoglycaemic treatment. This audit, however, indicates that recurrent

Table 1 Demographics and Synacthen test results in patients with diabetes mellitus and recurrent hypoglycaemia

Number	95
Male	46
Female	49
Age (years)	43.4 (10.4)
Synacthen test:	
Basal cortisol (nmol/l)	350 (150)
30 min cortisol (nmol/l)	734 (169)
60 min cortisol (nmol/l)	843 (168)
Peak cortisol (nmol/l)	848 (171)
Peak cortisol >500 nmol/l	94
Peak cortisol <415 nmol/l	1
Incremental cortisol response >200 nmol/l	94

Results are presented as mean (SD).

Table 2 Common clinical and laboratory features of Addison's disease[15]

Clinical feature (%)	Laboratory findings (%)
Anorexia, tiredness, fatigue (100)	U&E abnormalities (92)
Nausea, vomiting (75–86)	Hyponatraemia (88)
Abdominal pain (31)	Hyperkalaemia (64)
Constipation (33)	Uraemia (55)
	Normochromic normocytic anaemia (40)
Diarrhoea (16)	
Salt craving (16)	
Postural dizziness (12)	
Weight loss (100)	
Hyperpigmentation (94)	
Hypotension (90)	
Vitiligo (10–20)	

U&E, urea and electrolytes.

hypoglycaemia in patients with type 1 diabetes is only rarely due to Addison's disease.

A short Synacthen test is usually the initial endocrine investigation for adrenocortical insufficiency,[9] but it is time consuming, involves administration of parenteral ACTH, and may require admission to a day unit. The difficulty is predicting which diabetic patients with recurrent hypoglycaemia are unlikely to have Addison's disease in order to reduce the number of unnecessary short Synacthen tests. Addison's disease should be considered if typical clinical and biochemical features are present (table 2) and in the presence of other organ specific autoimmune disease, especially autoimmune thyroid disease.[11] Other than recurrent hypoglycaemia, our patient had none of characteristic features of Addison's disease or associated endocrinopathy (table 2) indicating that recurrent hypoglycaemia was the sole and perhaps early presenting feature of adrenal failure. This, therefore, suggests that Addison's disease should be considered as a cause of unexplained recurrent hypoglycaemia in all patients with type 1 diabetes. It has also been suggested that screening with 09.00 serum cortisol could reduce the number of unnecessary short Synacthen tests by 21%,[16] but this would involve the patient attending for venepuncture on at least two occasions if a short Synacthen test is necessary. An alternative approach would be to use adrenal antibodies to screen for Addison's disease, but doubts remain about their specificity since only 15% of diabetic subjects positive for adrenal antibodies have biochemical evidence of Addison's disease[12] and negative adrenal antibody status does not exclude Addison's disease.[17]

Our audit indicates that, although rare, recurrent hypoglycaemia in patients with type 1 diabetes mellitus may be the sole presenting feature of Addison's disease. We therefore suggest a low threshold for performing appropriate tests in patients with type 1 diabetes and recurrent hypoglycaemia is essential to detect Addison's disease.

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Conflict of interest: none stated

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